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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/836,455	05/09/1997	MALAYA CHATTERJEE	304142000322	6310

25226 7590 12/17/2003

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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 12/17/2003

37

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/836,455	CHATTERJEE ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,11,14-59,62,63 and 65-99* is/are pending in the application.

4a) Of the above claim(s) *1-5,20-37,39,40,42,43,46-56,67 and 68* is/are withdrawn from consideration.

5)☒ Claim(s) *6,11,14-18,38,57-59,62,63,65,66,70-75,79-88 and 90-98* is/are allowed.

6)☒ Claim(s) *19, 41, 44, 45, 69, 76-78, 89, and 99* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 11, 2003 in Paper No. 37 has been entered.

2. The amendment filed August 28, 2003 in Paper No. 38 is acknowledged and has been entered. Claims 7-10, 12, and 64 have been canceled. Claims 6, 11, 14, 15, and 82-88 have been amended. Claims 90-99 have been added.

3. The declaration under 37 CFR § 1.132 by Malaya Bhattacharya-Chatterjee filed August 28, 2003 as part of Paper No. 38 is acknowledged and has been entered.

4. The declaration under 37 CFR § 1.132 by Sunil K. Chatterjee filed August 28, 2003 as part of Paper No. 38 is acknowledged and has been entered.

5. Claims 1-6, 11, 14-59, 62, 63, and 65-99 are pending in the application. Claims 1-5, 20-37, 39, 40, 42, 43, 46-56, 67, and 68 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 14.

6. Claims 6, 11, 14-19, 38, 41, 44, 45, 57-59, 62, 63, 65, 66, and 69-99 are currently under prosecution.

Grounds of Objection and Rejection Withdrawn

7. Unless specifically reiterated below, the grounds of objection or rejection set forth in the Office action mailed February 11, 2003 (Paper No. 35) have been withdrawn.

The obviousness type double patenting rejection has been withdrawn in view of the restriction set forth in the Office action mailed September 4, 1998 between claims drawn to a nucleic acid molecule encoding a protein and claims drawn to the protein.

Claim Rejections - 35 USC § 101

8. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. Claims 19 and 77 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 19 and 77 are drawn to a host cell comprising the polynucleotide of claim 6, or claim 14, 15, 59, 71, 72, 73, 74, or 75, respectively. The claims are broadly interpreted to encompass host cells, which are not isolated and are comprised within an organism. Support for this interpretation of the claims can be found in the specification, e.g., at page 36, lines 14-27. Thus, the claims encompass host cells that have been transfected with the polynucleotide of claim 6, 14, 15, 59, 71, 72, 73, 74, or 75, which are comprised within a transgenic animal, including a human.

MPEP § 2105 [R-1] states:

> If the broadest reasonable interpretation of the claimed invention as a whole encompasses a human being, then a rejection under 35 U.S.C. 101 must be made indicating that the claimed invention is directed to nonstatutory subject matter.

10. Claims 41, 44, 45, and 99 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific and substantial asserted utility, a credible asserted, or a well-established utility.

The claims are drawn to an immunogenic composition comprising a nucleic acid molecule. The claims are interpreted as claims to a composition comprising the

polynucleotide of claims 6 or 90 that can be used to stimulate an immune response *against the nucleic acid molecule or some other component of the composition*, such as a vaccinia virus core protein of the immunogenic composition of claim 45. The utility of the anti-idiotypic antibody, which is encoded by the claimed nucleic acid molecules, is not questioned, as the specification asserts the antibody can be used to stimulate an anti-HMFG immune response. However, the specification does not appear disclose a utility for the claimed immunogenic composition; nor does the specification disclose a reason why one skilled in the art would use the claimed invention to stimulate an immune response against the nucleic acid molecule or some other component of the composition, such as a vaccinia virus core protein. Consequently, the Examiner does not know, and has not gleaned from the disclosure how the claimed immunogenic composition can be used by a relevant artisan in the "real-world", or in a manner that might provide immediate benefit to the public.

Because the specification does not disclose a currently available, "real world" use for the claimed immunogenic compositions, the requirements set forth under 35 U.S.C. § 101 have not been met. The existing information disclosed by Applicants' application would merely provide the artisan with an invitation to perform additional investigations, which might ultimately lead to the derivation of a specific benefit, or which might not. In either case, an immediate benefit could not be derived from the use of the claimed invention because the existing information is insufficient to enable the artisan to use the claimed immunogenic composition comprising the polynucleotide of claims 6 or 90 in the manner asserted to provide an immediate benefit.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 41, 44, 45, and 99 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility, a credible asserted utility, or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

13. Claims 19, 69, 77, and 89 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using an isolated host cell, does not reasonably provide enablement for any host cell encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 19 is drawn to a host cell comprising the polynucleotide of claim 6. Claim 77 is drawn to a host cell comprising the polynucleotide of any of claims 14, 15, 59, 71, 72, 73, 74, or 75, wherein said polynucleotide is recombinant. Claims 19 and 77 are broadly interpreted to encompass host cells, which are not isolated and are comprised within an organism. Support for this interpretation of the claims can be found in the specification, e.g., at page 36, lines 14-27. Thus, the claims encompass host cells that have been transfected with the polynucleotide of claim 6, 14, 15, 59, 71, 72, 73, 74, or 75 that are comprised within a transgenic animal, including nonhuman or human animals and animals treated using gene therapy.

Claims 69 and 89 are drawn to a methods for preparing a heavy or light chain variable region of antibody 11D10, wherein said method comprise expressing the polynucleotide of claims 73 and 72, respectively, in a host cell. Claims 69 and 89 are broadly interpreted to encompass methods comprising expressing a polynucleotide in host cells, which are not isolated and are comprised within an organism. Thus, the claims encompass methods, which comprise expressing the polynucleotide of claim 72 or 73 in host cells that have been transfected with said polynucleotides and which are comprised within a transgenic animal, including nonhuman or human animals and animals treated using gene therapy.

The teachings of the specification cannot be extrapolated to the enablement of the claimed invention because the amount of guidance, direction, and exemplification set forth therein would not be sufficient to enable the skilled artisan to have a reasonable expectation of success in making and using the claimed invention without the need to perform additional, and an undue amount of experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The specification does not provide a sufficient amount of guidance, direction, or exemplification to enable the skilled artisan to make or use host cells that are comprised within a non-human transgenic animal. In the art of producing transgenic animals, the phenotype of the resultant transgenic animal is not always predicable or viable. Houdebine (*Journal of Biotechnology* 1994, **34**: 269-287) teaches the vectors to be used for directing the expression of transgenes in any given tissue, or in all tissues, must contain the appropriate regulatory regions. Houdebine teaches expression is heavily dependent on the site of integration in the host genome and the site of integration is presently unpredictable. Therefore, it is concluded that one of skill in the art would need to perform undue experimentation in order to make and use the claimed host comprised within a transgenic animal.

In addition, the specification does not teach provide a sufficient amount of guidance, direction, and exemplification to enable the skilled artisan to have a reasonable expectation of successfully producing host cells within a living organism, which comprise the polynucleotide of claim 6, 14, 15, 59, 71, 72, 73, 74, or 75, by gene transfer, or *gene therapy*. The art of gene therapy, i.e., the *in vivo* delivery genetic information to targeted cells within a body using naked DNA or viral vectors or by reintroducing *ex vivo* modified host cells into the body, is still in its infancy. Moreover,

the art is highly unpredictable and its successful application has been hindered by numerous limitations, which the specification does not remedy and would preclude the skilled artisan from having a reasonable expectation of successfully making and using the claimed invention without need of performing an undue amount of experimentation.

For example, the teachings of the specification have not overcome the problems with *in vivo* delivery and expression. Verma et al. (*Nature* 1997, **389**: 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al. state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression. Similarly, Amalfitano et al. (*Current Gene Therapy* 2002, **2**: 111-133) teach that non-viral mediated transfer of DNA generally suffers from low transduction efficiencies. In addition, Amalfitano et al. discuss numerous limitations that have been encountered in using retroviral vectors to deliver DNA into a subject and teach the use of adenoviral vectors can be ineffective because of the induction of strong immune responses in the host to the viral vectors and direct acute and chronic toxicity caused by the vector itself.

It is noted that Amalfitano et al. teach that a despite general lack of success, the first conclusive evidence that gene therapy can show efficacy in humans was achieved in human X-linked SCID subjects *via* retrovirus transduction. However, since the publication, The Department of Health and Human Services has released a memorandum dated January 14, 2003, a copy of which is attached to this Office action, that urges all such investigations to be discontinued until new data are available, the possible etiology and risks of adverse events associated are considered, and recommendations emerge. Despite the initial promise of the trial studying gene transfer as a possible treatment for the disease, investigators have found that retroviral-mediated insertion of the transgene has caused the subjects to develop cancer. The results of the trial underscore the high degree of unpredictability associated with the art and the fact that the skilled artisan could not make or use the claimed invention with a reasonable expectation of success without need to perform additional experimentation.

The state of the art, as a whole, is well defined by Pandha et al. (*Current Opinion in Investigational Drugs* 2000; **1** (1): 122-134) in the abstract. Pandha et al. teach:

> Despite the rapid technological advances that continue to sustain the field of cancer gene therapy, few individual patients have benefited from the revolution so far. The plethora of clinical trials described confirms that each malignancy will have its own ideal strategy based on the associated molecular defects, and there has been rapid progress from this viewpoint. At the same time, there has been a renewed appreciation for the limitations to gene therapy, which include low efficiency of gene transfer, poor specificity of response and methods to accurately evaluate responses, and lack of truly tumor-specific targets at which to aim. As with all new therapies, we are climbing a steep learning curve in terms of encountering treatment-related toxicities, as well as profound ethical and regulatory issues.

In view of the preponderance of evidence establishing the state of the art, now and at the time the application was filed, and the level of unpredictability associated therewith, in the absence of a disclosure of an amount of guidance, direction, and exemplification that is reasonably commensurate in scope with the claims, it appears that skilled artisan could not make and use the claimed invention with a reasonable expectation of success without having the need to perform an undue amount of experimentation.

Amending claims 19, 69, 77, and 89 to recite "isolated" before "host cell" can obviate these grounds of rejection.

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 76 and 78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 76 presently depends from claim 64; and claim 64 has been canceled. Accordingly, the metes and bounds of the claimed subject matter cannot be ascertained.

Claim 78 presently depends from claims 7-10, 12, or 64; and claims 7-10, 12, or 64 have been canceled. Accordingly, the metes and bounds of the claimed subject matter cannot be ascertained.

Conclusion

16. The subject matter of claims 6, 11, 14-18, 38, 57-59, 62, 63, 65, 66, 70-75, 79-88, and 90-98 is allowable, provided that Applicants timely file a terminal disclaimer in compliance with 37 CFR 1.321(c) to overcome the actual and provisional rejections set forth above, which are based on a non-statutory double patenting ground, and the conflicting application and patent is shown to be commonly owned with this application. Claims 19, 41, 44, 45, 69, 76-78, 89, and 99 are not allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
December 15, 2003